REMARKS

Claims 1, 2, 5, 9, 10 and 21-25 were rejected. Claims 6-8 and 11-20 have been withdrawn from consideration. Claims 21-25 are cancelled and claims 1, 11, 12, 16 and 17 amended. The amendments are supported throughout the application, for instance by pages 68 (last two paragraphs) to page 69 (line 6), page 73 (lines 5-6 and 12-13), page 84 (line 19) to 85 (line 6) of the specification and the claims as originally filed. No new matter is added. Claims 1, 2, 5, 9, 10 and 21-25 are therefore submitted for further consideration at this time. Applicants respectfully request reconsideration and withdrawal of all rejections.

Claim Rejections - 35 U.S.C. 103

Claims 1, 2, 9, 10 and 21-25 were rejected under 35 U.S.C. 103 as being obvious over Merck Index #4852 (Merck) and Morikawa et al. It is alleged in the Office Action that those of ordinary skill in the art would have been motivated to employ indomethacin esters for the same therapeutic use as claimed with a reasonable expectation of success.

Applicants respectfully disagree. Applicants point out that present invention is directed to methods for the treatment of urinary incontinence by administering the nitro-oxy derivative of indomethacin (NOI). While Merck teaches indomethacin as useful for treating inflammation, the Patent Office at page 3 of the Office Action indicates that Morikawa et al. discloses indomethacin as being useful for increasing the time of micturition and increasing bladder pressure. Applicants wish to emphasize however that the present application includes *in vivo* experiments assaying those same

parameters considered by Morikawa et al. in evaluating indomethacin, that is, the time of micturition and bladder pressure threshold. Accordingly, it is quite possible to compare indomethacin with the NOI compound of the present invention, in those pharmacological tests considered by the Patent Office to be important for assessing the activity of indomethacin in urinary incontinence. Applicants respectfully submit that in light of such comparison as discussed below, the use of the NOI compounds in methods as claimed are not taught or suggested by any combination of the cited Merck and Morikawa et al. references, and such methods should be considered patentable at least by virtue of unexpected results not taught or suggested.

Regarding time or frequency of micturition, Applicants point out that at least two pharmacological experiments are reported in the present application. First, with reference to Examples 4C and 5 as well as Table 2, Applicants note that conscious rats were orally treated with indomethacin and NOI at a dose of 5 mg/Kg each. The bladders of the animals were filled with physiological solution and the intervals between bladder contractions determined. Applicants wish to emphasize that the 5 mg of compound corresponds to 0.014 moles of indomethacin (m.w. 357.79) and 0.0098 moles of NOI (m.w. 508.92). In other words, 5 mg of compound contains more moles of indomethacin as compared to the NOI compound. Indeed, the molar amount of administered NOI compound is 70% that of indomethacin (0.014 - 0.0098 / 0.014), or nearly 2/3 the molar dose.

Table 2 reports the frequency of micturition, or intervals between contractions, after compound administration versus a baseline, the baseline corresponding to intervals between contractions prior to compound administration. As noted by the

Patent Office at page 4 of the Office Action, the difference between the results obtained with NOI and indomethacin is about 10%. However, this difference is related to the administration of the same weight-dose of the compounds, or in other words, the molar dose is higher with regard to indomethacin, as demonstrated above.

Second, with reference to Examples 9D and 10 and Table 5, experiments were performed on female Beagle dogs in substantially in the same way as described above. The administered doses of both indomethacin and NOI were 3 mg/Kg. The molar amount of NOI was therefore again significantly lower as compared to indomethacin. As can be seen from Table 5, the response for the group treated with NOI was 14% higher than for the group treated with the indomethacin. Again, a significantly improved response was achieved where the administered molar amount of NOI was significantly lower as compared to indomethacin.

Applicants respectfully submit that such improved results are not taught or suggested in the prior art. Applicants point out that those of ordinary skill in the art would not expect that by administering an indomethacin derivative in a dose corresponding, on a molar basis, to about 70% of that of the indomethacin parent, the derivative would result in a pharmacological response over 10% higher than that obtained with indomethacin. In fact, it is well known to those of ordinary skill in the art that analogs, homologs, isomers, bioesters, salts, acids and esters of a compound do not ordinarily behave in this way. Analogs, homologs and other derivatives of parent compounds simply do not ordinarily display such significant increases in activity when administered at a molar dose significantly lower than the parent compound. Such

results as provided by the claimed invention are simply unexpected in light of the prior art.

Moreover, with respect to bladder pressure threshold as disclosed by Morikawa et al., Applicants point out that the present application discloses experiments performed on rats, where the urinary bladders were progressively filled with a physiological solution. See pages 52-53 of the Specification. The volume of physiological solution and the pressure threshold required to evoke the reflex were determined. Applicants point out that the same dose of 3 mg/Kg for both indomethacin and NOI were administered to the animals. Accordingly, the molar amount of NOI was again 70% of that of the indomethacin. Nevertheless, as indicated in Table 3, both the pressure and volume threshold increase was significantly higher for NOI as compared to indomethacin, in particular an increase of 17% for pressure threshold and 14% for volume threshold. Again, such improved activity with NOI of only about 70% of indomethacin cannot be considered taught or suggested by the prior art. Such improved results as obtainable by the claimed invention can only be considered unexpected in light of the knowledge in the art.

It is also noted that the Patent Office has alleged that tests for data reliability have not been provided. However, Applicants respectfully submit that all experiments were performed according to well known and established pharmacological methods, using the stocks and number of animals normally employed in said experiments. See pages 51 (second paragraph under Table 1), 53 (lines 9-11) and page 56 (lines 5-8). Such methods are considered by those of ordinary skill in the art to produce reliable results. Applicants therefore submit that the obtained data, being the average of single

determinations, reliably demonstrates the significant and unexpected improvement in pharmacological response obtainable by the methods and NOI compounds of the claimed invention as compared to the use of indomethacin. Applicants urge that all rejections should be withdrawn.

Applicants also note that the Patent Office is of the opinion that it is well known in the art that carriers and excipients are employed to enhance the activity of active ingredients. However, it is respectfully pointed out that each of the compounds of the experiments described above were orally administered in a carboxymethyl cellulose suspension. See e.g., page 49 (lines 17-18) of the Specification. Applicants respectfully point out that this suspension is of general use in the art, and moreover, that the suspension was used for both NOI and indomethacin, the suspension therefore producing any effect similarly for both compounds. The improved response obtainable by the claimed invention remains quite unexpected as compared to the prior art.

Finally, Applicants point out that in the Amendment of May 14, 2001, the efficacy of indomethacin was further compared to the NOI derivative. With reference to Table 1 and Example 3, it is demonstrated that the NOI derivative inhibits contraction by 48.1%, in contrast to an efficacy of indomethacin at 38.5%. That is, the claimed invention is nearly 25% more efficient than the cited prior art. Again, it is demonstrated that the methods of the claimed invention, as seen by comparison testing, are capable of dramatically improved and unexpected results as compared to the prior art.

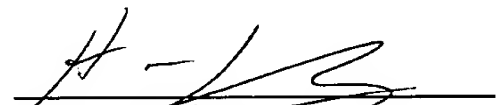
Applicants therefore respectfully submit that the results of the comparative experiments clearly demonstrate that NOI compounds in the claimed invention at the very least are significantly more active than indomethacin in all the tests performed. As

a consequence, the methods as claimed with NOI are superior than the indomethacin compound in the treatment of urinary incontinence. Such results are simply unexpected in light of the prior art, and therefore all rejections should be withdrawn.

In light of the discussion above, Applicants respectfully submit that the claimed invention is in condition for allowance.

In case this paper is not timely filed, the undersigned hereby petitions for an appropriate extension of time. Please charge any fee deficiency or credit any overpayment to Deposit Account No. 01-2300.

Respectfully submitted,



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1. (Amended) A method for treatment of urinary incontinence by administering compounds, having the formula:

$$A\text{-}X_1\text{-}NO_2$$

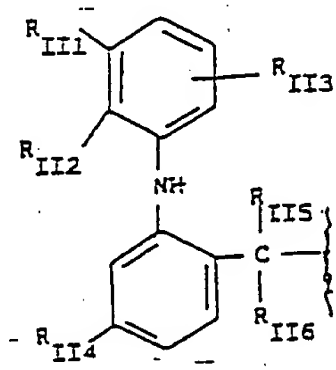
or their salts, where:

A = $R(COX)_t$ wherein t is an integer 0 or 1;

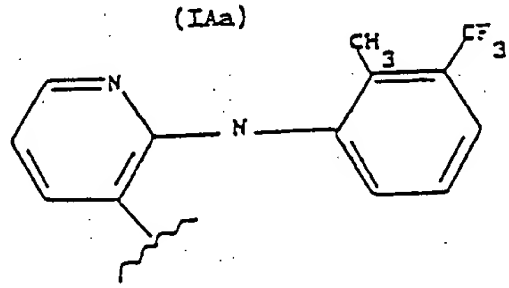
X = O, NH, NR_{1C} wherein R_{1C} is a linear or branched alkyl having from 1 to 10 C atoms;

R is chosen from the following groups:

Group I A), where t = 1,



(IAa)



(IAb)

where:

R_{II5} is H, a linear C_1-C_3 alkyl, or a branched C_1-C_3 alkyl;

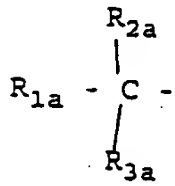
R_{II6} has the same structure as R_{II5},

R_{II1}, R_{II2} and R_{II3} are each hydrogen, linear C_1-C_6 alkyl, branched C_1-C_6 alkyl, C_1-C_6 alkoxy, Cl, F, or Br;

R_{II4} has the same structure as R_{II1} or is bromine;

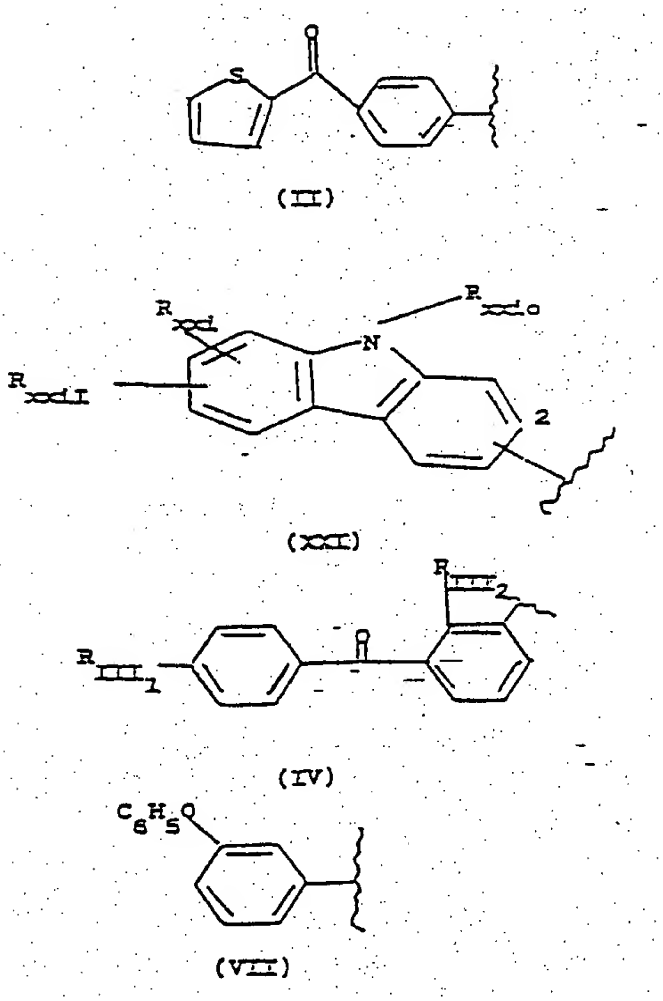
Group II A) chosen from the following:

where, when t = 1, R is



where R_{2a} and R_{3a} are H, a linear C_1-C_{12} alkyl, a branched C_1-C_{12} alkyl, or allyl, with the proviso that when one of the two is allyl the other is H;

R_{1a} is chosen from the subgroup II Aa) consisting of

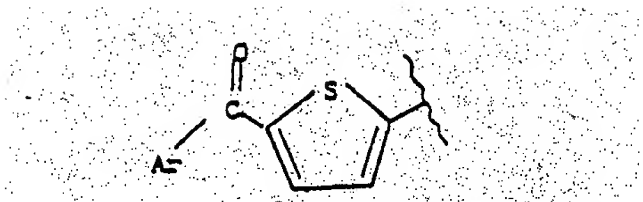


(II)

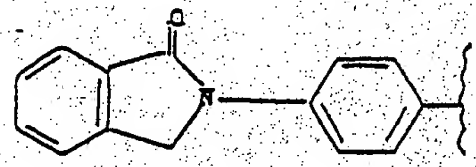
(XXI)

(IV)

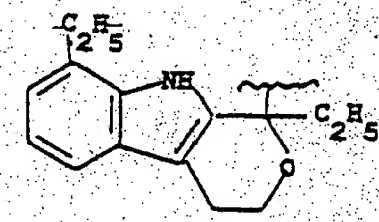
(VII)



(XXXV)



(VI)



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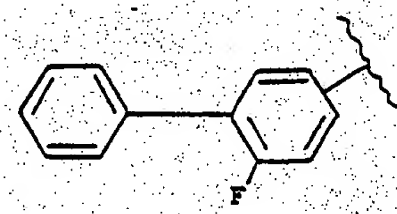

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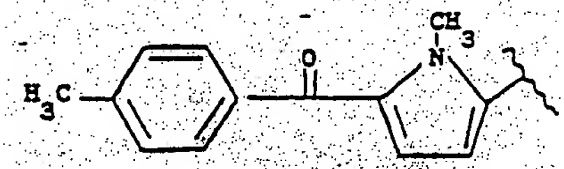
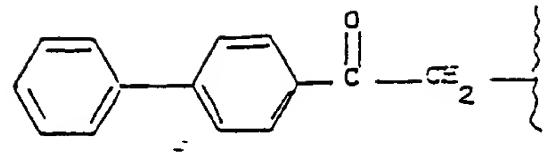


(X)

, and



(III)

wherein:

in the residue of formula (IV):

R_{III1} is H or SR_{III3} where R_{III3} contains from 1 to 4 linear or branched C atoms; and

R_{III2} is H or hydroxy;

in the residue of formula (XXI):

R_{xxio} is H, a linear alkyl having 1-6 carbon atoms, a branched alkyl having from 1 to 6 carbon atoms, a C_1-C_6 alkoxy-carbonyl bound to a C_1-C_6 carboxyalkyl, or a C_1-C_6 alkanoyl, optionally substituted with halogen, benzyl or halobenzyl, benzoyl or halobenzoyl;

R_{xxi} is H, halogen, hydroxy, CN, a C_1-C_6 alkyl [, a C_1-C_6 alkyl,] optionally containing OH groups, a C_1-C_6 alkoxy, acetyl, benzyloxy, SR_{xxi2} where R_{xxi2} is a C_1-C_6 alkyl; a perfluoroalkyl having a 1-3 C atoms, a C_1-C_6 carboxyalkyl optionally containing OH groups, NO_2, sulphamoyl, dialkyl sulphamoyl with the alkyl having from 1 to 6 C atoms, or difluoroalkylsulphonyl with the alkyl having from 1 to 3 C atoms;

R_{xxil} is halogen, CN, a C_1-C_6 alkyl optionally containing one or more OH groups, a C_1-C_6 alkoxy, acetyl, acetamido, or benzyloxy,

SR_{III3} is as above defined, a perfluoroalkyl having from 1 to 3 C atoms, hydroxy, a carboxyalkyl having from 1 to 6 C atoms, hydroxy, a carboxyalkyl having from 1 to 6 C atoms, NO_2, amino, mono- or dialkylamino having from 1 to 6 C atoms, sulphamoyl, a

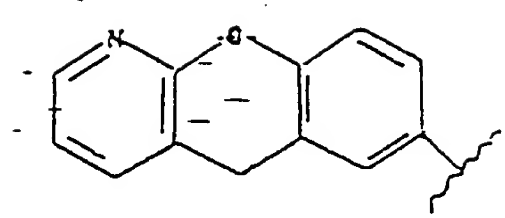
dialkyl sulphamoyl having from 1 to 6 C atoms, difluoroalkylsulphamoyl; or R_{xxi} together with R_{xxii} is an alkylene dioxy having from 1 to 6 C atoms;

In the residue of formula (XXXV):

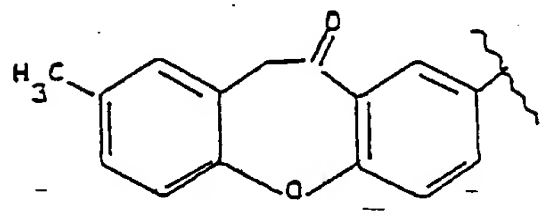
Ar is phenyl, hydroxyphenyl optionally mono- or polysubstituted with halogen, an alkanoyl or alkoxy having from 1 to 6 C atoms, a trialalkyl having from 1-6 C atoms, cyclopentyl o-hexyl o-heptyl, thienyl, furyl, furyl containing OH, or pyridyl;

Subgroup II Ab) consisting of:

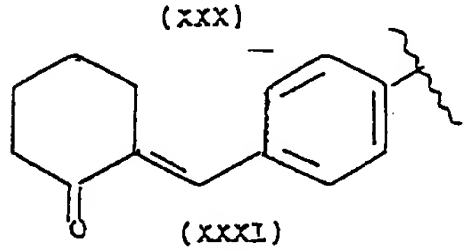
II Ab) :



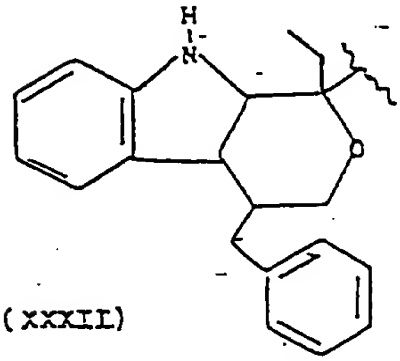
IIIa)



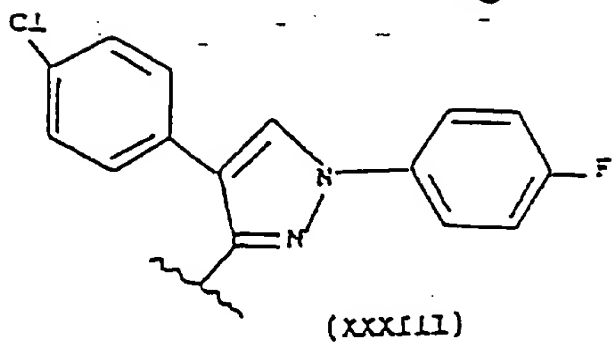
(XXX)



(XXXI)



(XXXII)



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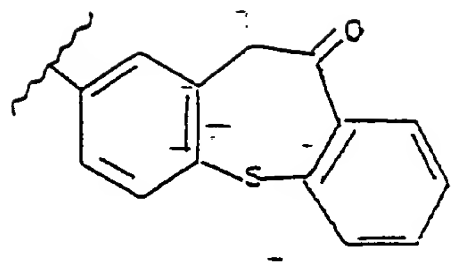

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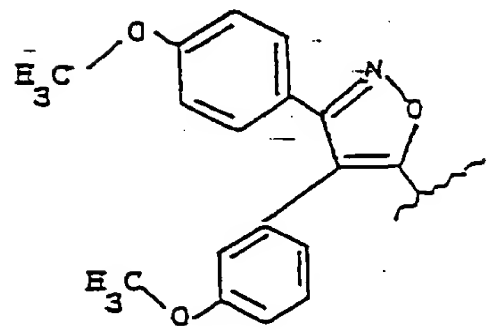


(XXXVII)

wherein:

when IIIa) contains -CH(CH_3)-COOH it is known as pranoprofen: α-methyl-5H-(1) benzopyran (2,3-b) pyridine-7-acetic acid;

when residue (XXX) contains -CH(CH_3) -COOH it is known as bermoprofen: dibenz (b,f) oxepin-2-acetic acid;

residue (XXXI) is known as CS-670: 2-(4-2(2-oxo-1-cyclohexylidenemethyl) phenyl) propionic acid, when the radical is -CH(CH_3) -COOH;

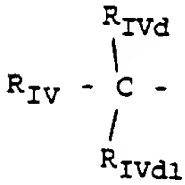
when residue (XXXII) contains group -CH_2COOH it is known as pemedolac;

when residue (XXXIII) is saturated with -CH_2COOH it is known as pyrazolac: 4-(4-chlorophenyl)-1-(4-fluorophenyl) 3-pyrazolyl acid derivatives;

when residue (XXXVI) is saturated with -$CH(CH_3)$-COO- it is known as zaltoprofen;

when residue (XXXVII) is CH_2-COOH it derives from the known mofezolac: 3,4-di p-methoxyphenyl) isoxazol-5-acetic acid;

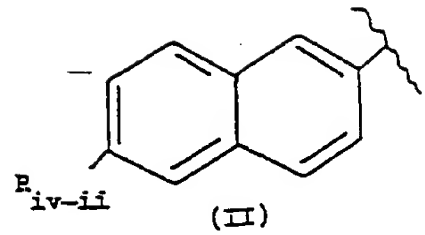
Group IIIA), where t = 1,



wherein:

at least one of R_{Ivd} and R_{Ivd1} is H and the other a linear or branched C_1-C_6 alkyl, or difluoroalkyl with the alkyl having from 1-6 C atoms, or R_{Ivd} and R_{Ivd} jointly form a methylene group;

R_{IV} has the following structure:



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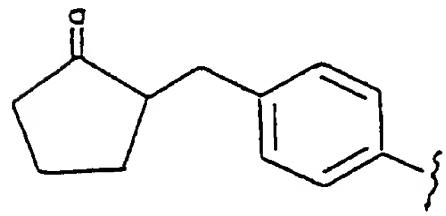
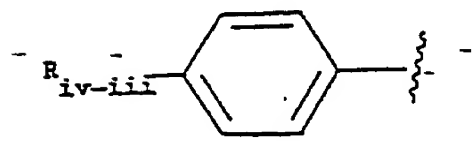


(X)

, or



(III)

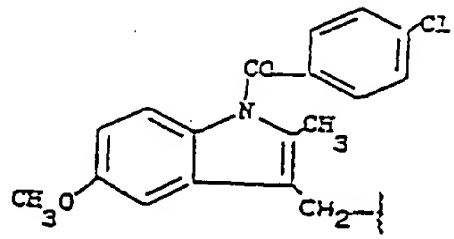
where:

in the residue of formula (II):

R_{IV-II} is selected from the group consisting of an alkyl having from 1 to 6 C atoms, a cycloalkyl having from 3 to 7 C atoms, an alkoxymethyl having from 1 to 7 C atoms, a trifluoroalkyl having from 1 to 3 C atoms, vinyl, ethynyl, halogen, an alkoxy having from 1 to 6 C atoms, a difluroalkoxy with the alkyl having from 1 to 7 C atoms, an alkoxymethyloxy having from 1 to 7 C atoms, an alkylthiomethyloxy with the alkyl having from 1 to 7 C atoms, an alkylmethylthio with the alkyl having from 1 to 7 C atoms, cyano, difluoromethylthio, a substituted phenyl-, and phenylalkyl with the alkyl having from 1 to 8 C atoms;

$R_{IV\text{-}III}$ is a C_2-C_5 alkyl, a C_2 or C_3 alkyloxy, allyloxy, phenoxy, phenylthio, a cycloalkyl having from 5 to 7 C atoms, optionally substituted at position 1 by a C_1-C_2 alkyl;

Group IV A)

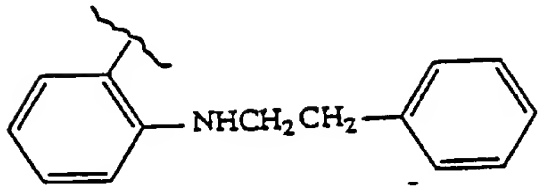


(IV)

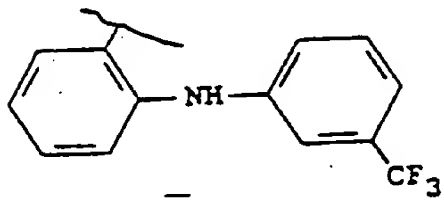
where A = RCOO, t = 1,

Group V A) chosen from the following:

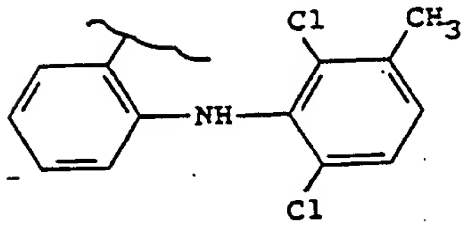
Subgroup V Aa) residues chosen from the following, where t = 1



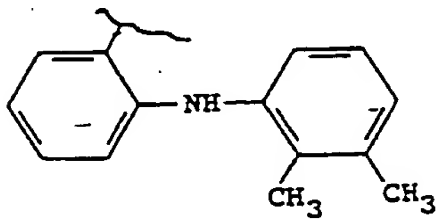
(V Aa1)



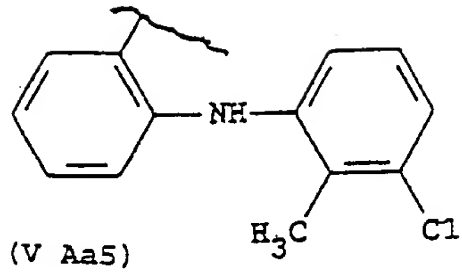
(V Aa2)



(V Aa3)

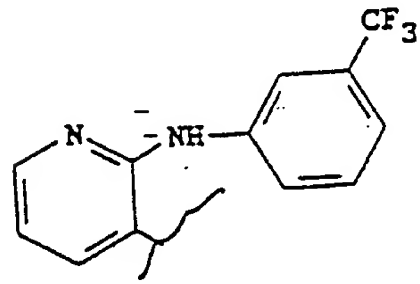


(V Aa4)



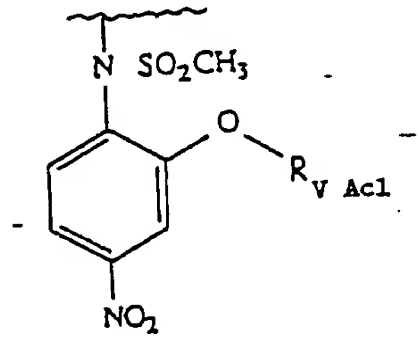
(V Aa5)

subgroup V Ab), residue, where t = 1:

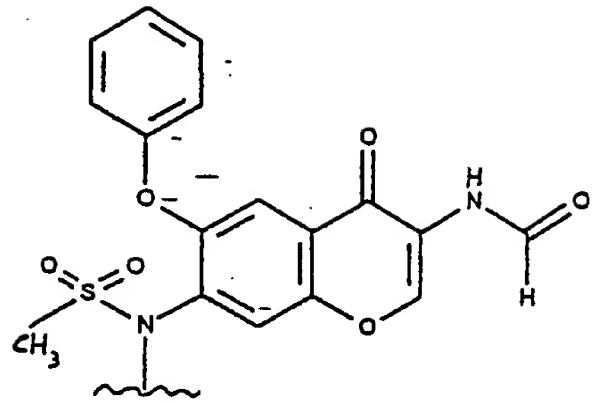


(V Ab1)

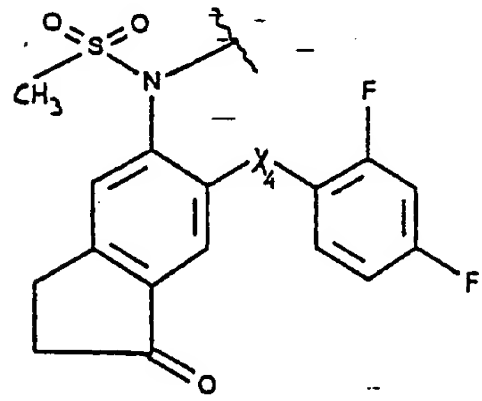
subgroup V Ac), residue, where t = 0 and R is as follows:



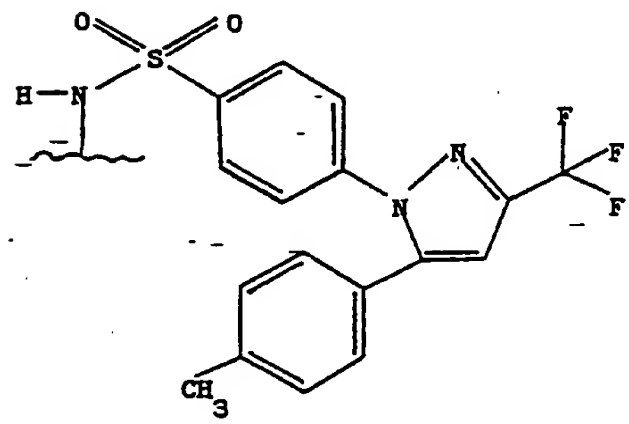
(V Ac1)



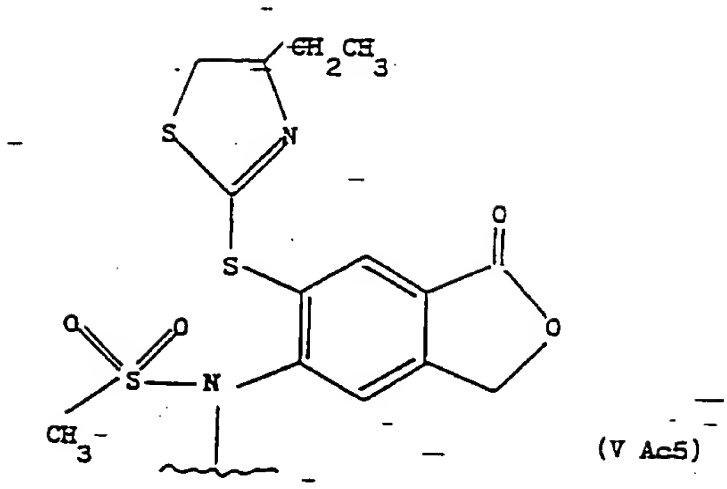
(V Ac2)



(V Ac3)

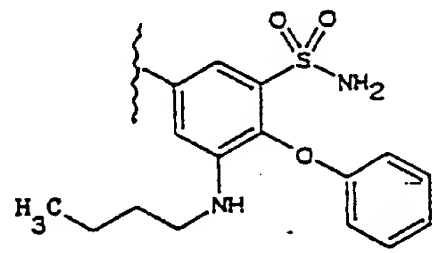


(V Ac4)

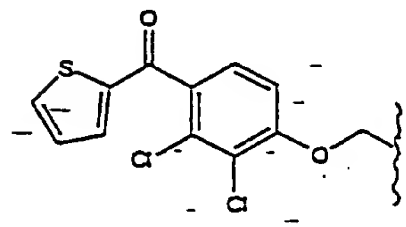


(V Ac5)

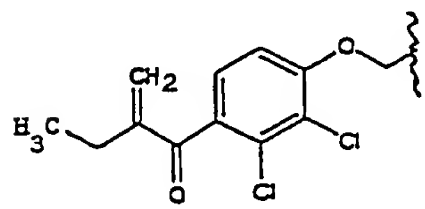
subgroup V Ad) residues, where t = 1 and R is as follows:



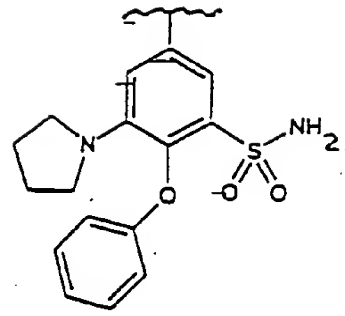
(V Ad1)



(V Ad2)

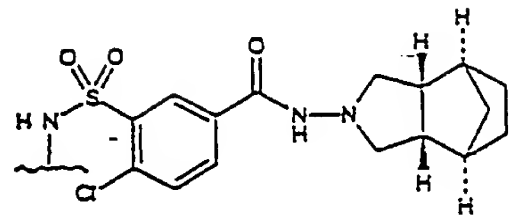


(V Ad3)

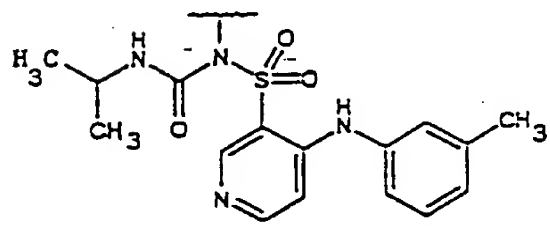


(V Ad4)

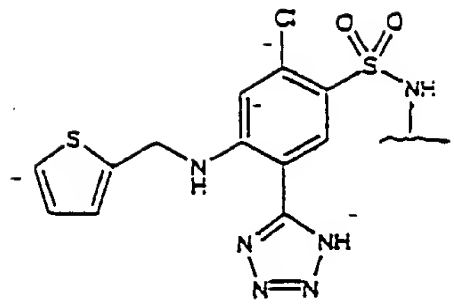
subgroup Ae) residues, where t = 1 and R is as follows:



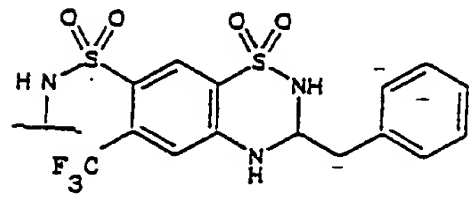
(V Ae1)



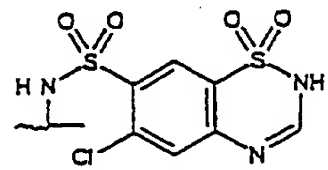
(V Ae2)



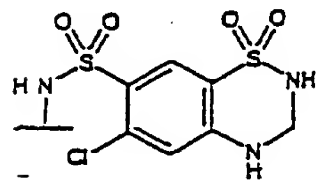
(V Ae3)



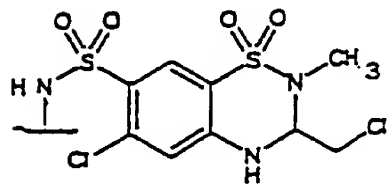
(V Ae4)



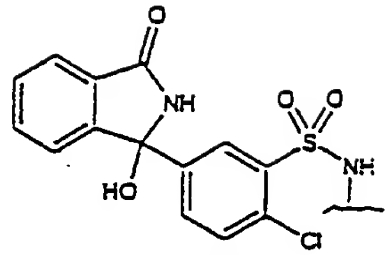
(V Ae5)



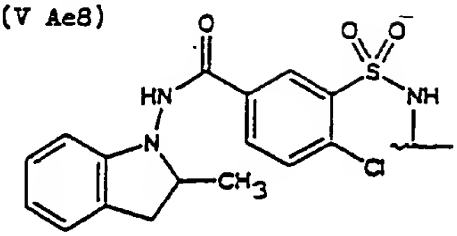
(V Ae6)



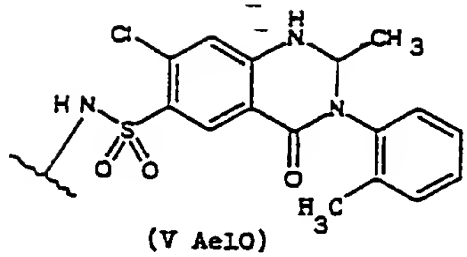
(V Ae7)



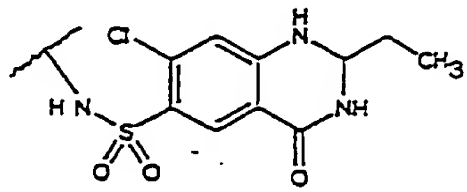
(V Ae8)



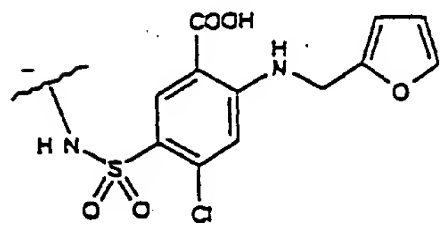
(V Ae9)



(V Ae10)



(V Ae11)



(V Ae12)

wherein:

[in residue (V Ac1) Rvac1 is phenyl or cycloexane;

in compounds (V Ac2) the residue is 3-formylamino-7-methylsulfonylamino-6-phenoxy-4H-1-bezopyran-4-one;

in residue, (V Ac3), X_4 is sulfur or oxygen;]

in compounds (V Ac1) Rvac1 attached to the oxygen atom in position 2 of the benzene ring of the N - (4-nitro-phenyl)methansulphonamide can be phenyl or cyclohexane, when Rvac1 is phenyl the residue is that of nimesulfide;

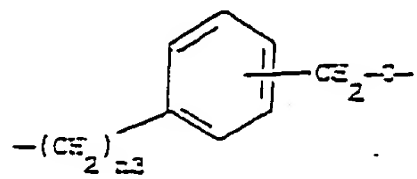
in compounds (V Ac2) the residue of 3-formylamino-7-methylsulfonylamino-6-phenoxy-4H-1-bezopyran-4-one has been shown;

in compounds (V Ac3) the atom X_4 that links the radical 2,4-difluorothiophenyl to position 6 of the indanone ring of the residue 5-methanesulfonamido-1-indanone can be sulfur or oxygen;

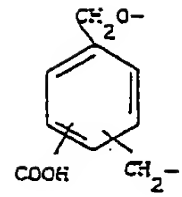
X_1 in formula A-X_1-NO_2 is a bivalent connecting bridge chosen from the following:

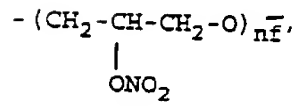
- YO

where Y is a linear or branched C_1-C_{20} alkylene, or an optionally substituted cycloalkylene having from 5 to 7 carbon atoms;

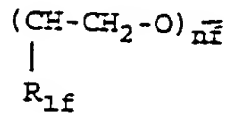


where n_3 is an integer from 0 to 3;





where nf' is an integer from 1 to 6;



where R_{1f} = H or CH_3 and nf is an integer from 1 to 6.

11. (Amended) The method of claim 1, wherein in formula (Iaa) R_{II1}, R_{II2} and R_{II4} are H, and

R_{II3} is chlorine and R_{II3} is in the ortho position to NH;

R_{II5} and R_{II6} are H,

X is equal to O, and

X_1 is $(CH_2 - CH_2 - O)_2$

[wherein R_{II1}, R_{II2} and R_{II4} are H;

R_{II3} is C1 and R_{II3} is in the other position to NH;

R_{II5} and R_{II6} are H;

X equals O; and

X_2 is $(CH_2 - CH_2 - O)_2$].

12. (Amended) The method of Claim 11, wherein in formula A = $R(COX)_t$ R is chosen from group IA) X = O

[wherein X equals O].

16. (Amended) The method of claim 1, wherein

[Ar is phenyl;

R_{3a} is H;

R_{2a} is methyl; and

X is O]

X of $A=R(COX)_t$ is O and in group IIA):

in the residue R_{1a} of formula (IV) R_{III1} and R_{III2} are H, R_{3a} is H, and R_{2a} is methyl;

in the residue R_{1a} of formula (XXI) R_{xxio} is H, the connecting bridge X_1 is at position 2, R_{xxi} is H, R_{xxi1} is chlorine and is in the para position to nitrogen; R_{3a} is H, R_{2a} is methyl;

in the residue R_{1a} of formula (XXXV) Ar is phenyl, R_{3a} is H, R_{2a} is methyl;

R_{1a} is the residue of formula (II) R_{3a} = H, R_{2a} = CH_3;

R_{1a} is the residue of formula (VI), R_{2a} is CH_3 or H, R_{3a} = CH_3;

R_{1a} is the residue of formula (VIII), R_{3a} = R_{2a} =H;

R_{1a} is the residue of formula (VII), R_{3a} = H, R_{2a} = CH_3;

R_{1a} is the residue of formula (III), R_{3a} = R_{2a} = H;

R_{1a} is the residue of formula (X), R_{3a} = R_{2a} = H;

R_{1a} is the residue of formula (IX), R_{3a} = H, R_{2a} = CH_3.

17. (Amended) The method of claim 1, wherein [:

$R_{IV\text{-}II}$, is CH_3O, R_{IVd}, is H, and

R_{IVd1} is CH_3]

X in $A=R(COX)_t$ is NH, O;

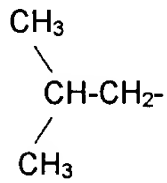
X_1 is $(CH_2)_4$ or $(CH_2CH_2O)_2$;

and in group IIIA):

R_{IV} is the residue of formula (II) wherein $R_{IV\text{-}II}$ is CH_3O, R_{IVd} is H and R_{IVd1} is CH_3;

R_{IV} is the residue of formula (II) wherein R_{IVd} is H, R_{IVd1} is CH_3, X = NH or O;

R_{IV} is the residue of formula (III) wherein $R_{IV\text{-}III}$ is



R_{IVd} = H, R_{IVd1} is CH_3.